SMALL-MOLECULE BOTULINUM TOXIN INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to U.S. Application Ser. No. 61/229,827, filed on Jul. 30, 2009.

STATEMENT AS TO FEDERALLY FUNDED RESEARCH

Studies described herein were supported by the U.S. Army Medical Research Acquisition Activity (W81XWH-04-2-0001) and (W81XWH-08-1-0154), the U.S. Army Research Office (W911NF-09-1-0095), and the U.S. Defense Threat Reduction Agency (3.10023_07_RD_B and 3.10014_08_WR_B). The Government has certain rights in this invention.

TECHNICAL FIELD

This disclosure relates to materials and methods for inhibiting Botulinum neurotoxin, and more particularly to materials and methods for inhibiting the zinc endopeptidase of Botulinum neurotoxin serotypes A, D and/or E (BoNTA, BoNTD and/or BoNTE).

BACKGROUND

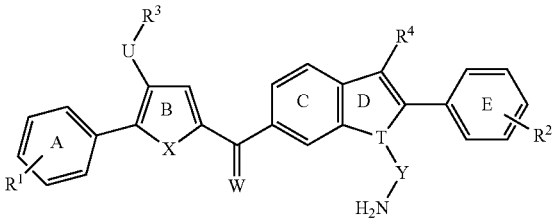
Botulinum neurotoxin serotype A (BoNTA) is a highly toxic by-product of a naturally occurring, spore-forming anaerobic bacterium (*Clostridium botulinum*). BoNTA inhibits the release of acetylcholine from presynaptic nerve terminals at neuromuscular junctions, causing flaccid paralysis and leading to death by respiratory arrest. BoNTA also can be used in the treatment of various muscular dysfunctions and has been widely used as a cosmetic known as BOTOX® to diminish facial lines. BoNTA, however, is fatal when misused, and there are currently no chemical antidotes to BoNTA.

The crystal structure of holo BoNTA includes two polypeptide chains that are linked by a disulfide bond. The light chain (50 KDa) is a zinc endopeptidase that specifically cleaves neuronal proteins responsible for acetylcholine release. The heavy chain (100 KDa) mediates selective binding to neuronal cells via specific gangliosides and translocates the light chain into the cytosol after receptor-mediated endocytosis of the entire molecule. Of eight serotypes of BoNT, serotypes A, D and E are closely related, according to sequence analysis using ClustalW.

SUMMARY

This disclosure provides materials and methods for inhibiting Botulinum neurotoxin, including BoNTA, BoNTD, and/or BoNTE. For example, small-molecule inhibitors of BoNTA are provided. A small-molecule inhibitor can inhibit the zinc protease, an endopeptidase, of BoNTA, BoNTD, and/or BoNTE. In some cases, a small-molecule inhibitor can inhibit the zinc protease of BoNTA. Methods for using such small-molecule inhibitors to treat, prevent, or ameliorate one or more symptoms of Botulinum poisoning or disorders associated with Botulinum poisoning, including food-borne botulism, infant botulism, wound botulism, adult enteric infectious botulism, and inhalation botulism, and BoNTA, BoNTD, and/or BoNTE poisoning, are also provided. Kits and articles of manufacture containing one or more small-molecule inhibitors and accessory items are also provided.

Provided herein is a composition having a compound of Formula (I-A):



or a pharmaceutically acceptable salt or derivative thereof, wherein:

R^1 is chosen from OH and NH_2;

R^2 is chosen from H, OH, halo, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{1\text{-}10}$ alkoxy, cycloalkyl, aryl, heteroaryl, $CONH_2$, and $CONR^{2a}R^{2b}$;

R^{2a} and R^{2b} are independently chosen from $(CH_2)_{m3}NH_2$;

m3 is an integer from 4 to 12;

R^3 is chosen from thiol, imidazole, sulfonamide, COOH, and CONHOH;

R^4 is chosen from H, F, Cl, and Br;

X is chosen from S, NH, and O;

T is chosen from C and N;

U is chosen from $(CH_2)_{m1}V(CH_2)_{m2}$;

V is chosen from C, C(OH), O, S, and NH, or is absent;

m1 is an integer from 0 to 3;

m2 is an integer from 0 to 3;

W is chosen from O and S;

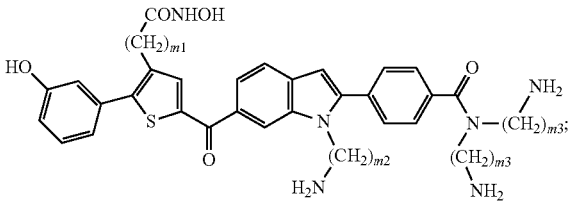
Y is chosen from $CO(CH_2)_{m4}$, $(CH_2)_{m4}$, and $CONH(CH_2)_{m4}$;

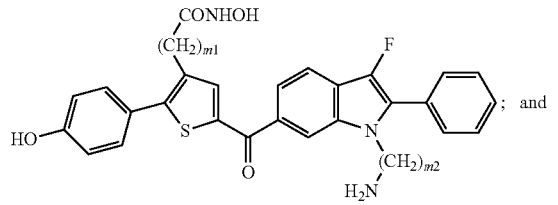
m4 is an integer from 2 to 8;

all non-hydrogen atoms in rings A-E can be substituted by N, S, or O provided the substitution maintains aromaticity; and

wherein if R^4 is H then R^2 is not H.

In some embodiments, a compound of Formula (I-A) is chosen from:





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